AF

PATENT SPECIFICATION

NO DRAWINGS

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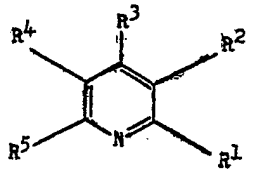
COMPLETE SPECIFICATION

Fluoropyridines

We NATIONAL RESEARCH DEVELOPMENT CORPORATION, a British Corporation, Established by Statute, of Kingsgate House, 66 Victoria Street, London, S.W.1., and formerly of 1 Tilney Street, London, W.1., do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement: —

The present invention relates to a method of preparing fluoropyridine carboxylic acids.

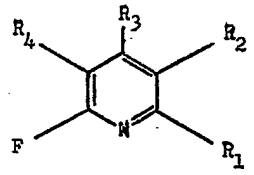
Our co-pending Application No. 10381/64 (Serial No. 1,107,881) provides a process for the preparation of a fluorinated pyridine compound of the formula:



(I)

wherein R^1, R^2, R^3, R^4 and R^5 represent fluorine atoms, or wherein R^2 and/or R^4 represent chlorine atoms whilst the remaining R groups represent fluorine atoms, or wherein R^4 represents a hydrogen atom, R^2 represents a chlorine atom and the remaining R groups represent fluorine atoms, which process comprises heating pentachloropyridine or tetrachloropyridine with anhydrous potassium fluoride in the absence of a solvent. This co-pending Application also discloses that 2, 3, 5, 6-tetrafluoroisonicotinic acid can be prepared by carbonylation of a Grignard reagent prepared from 4-bromotetrafluoropyridine.

The present invention provides a process for the production of a fluoro pyridine carboxylic acid or dicarboxylic acid of the formula



(II)

wherein one of the symbols R_1, R_2, and R_3 represents a carboxy group whilst the remaining symbols represent fluorine atoms, and R_4 represents a fluorine atom or, when R_2 represents a carboxy group, R_4 can represent a fluorine or hydrogen atom or a carboxy group, which process comprises converting 2,4,6-trifluoropyridine or a tetrafluoropyridine into the corresponding lithium derivative at a low temperature, reacting the lithium derivative with carbon dioxide, and hydrolysing the resulting product.

The trifluoro or tetrafluoropyridine compounds used according to the present invention can be obtained by a process which comprises reacting hydrogen with compounds of formula (II) wherein R_1, R_2, R_3 and/or R_4 represents fluorine and chlorine atoms, in the presence of a hydrogenation catalyst, prefer-

[*Price* 4*s*. 6*d*.]

ably palladised charcoal. Hydrogenolysis of pentafluoro pyridine, 3-chloro tetrafluoro pyridine or 3,5-dichlorotrifluoro pyridine, for instance in the presence of 10% palladium on charcoal, leads to the formation of trifluoro and tetrafluoro pyridines, chlorine atoms being hydrogenolysied in preference to fluorine atoms, and fluorine atoms at position -4 in preference to those in other positions. Specific examples of this hydrogenolysis include the conversion of 3-chlorotetrafluoropyridine into 2,5,6,-trifluoro- and 2,4,5,6,-tetrafluoropyridine; the conversion of 3,5-dichloro trifluoropyridine into 2,4,6-trifluoropyridine and the conversion of pentafluoropyridine into 2,4,5,6-, 2,3,5,6,- and 3,4,5,6-tetrafluoropyridine.

The hydrogen atoms in the hydrogenolysed compounds can be replaced by lithium atoms by exchange reactions, with, for example butyl lithium or methyl lithium, conveniently in an inert organic solvent such as hexane, tetrahydrofuran or diethyl ether and then reacted with carbon dioxide.

The three tetrafluoropyridines readily form the corresponding 2-lithium-, 3-lithium- and 4-lithium-tetrafluoropyridines and these, when carbon dioxide is passed in, are converted respectively into tetrafluoropicolinic acid, tetrafluoronicotinic acid and tetrafluoroisonicotinic acid. Similarly, when 2,4,6-trifluoropyridine is reacted with 1 mol of butyl lithium and then treated with carbon dioxide, 2,4,6-trifluoronicotinic acid is formed whilst the use of 2 mols of butyl lithium followed by the carbon dioxide treatment leads to the formation of 3,5-dicarboxy-2,4,6-trifluoropyridine. Having regard to the provisions of Section 9 of the Patents Act 1949, attention is directed to Patents No. 1100824 and 1100825.

Example 1

Reduction of 3-Chlorotetrafluoropyridine

3-Chlorotetrafluoropyridine was dropped at a rate varying between 0.2 g/min. and 0.1 g/min. into a flask heated at 200°C through which a stream of hydrogen (50 ml/min.) was passing. The chlorofluoropyridine vaporised immediately and was carried on the stream of hydrogen through a silica tube 1" in diameter and 12" long. The central 6" of this tube was heated by an electric furnace and was packed with palladised charcoal (10% Pd and 90% C) which was held in position by glass wool plugs and heated to 250°C. The emergent mixture was condensed, dried by vacuum distillation from phosphorus pentoxide and purified by vapour phase chromatography. It contained 70 to 80% by weight of 2,4,5,6-tetrafluoropyridine (Found: C,40.1, F,49.9% C_5NHF_4 requires C, 39.74, F, 50.3%) and approximately 5% by weight of 2,5,6-trifluoropyridine. The structure of the tetrafluoropyridine was confirmed by its nuclear magnetic resonance spectrum.

Example 2

Reduction of 3,5-Dichlorotrifluoropyridine

Using the same technique as in Example 1 but heating 3,5-dichloro-trifluoropyridine to 240°C the latter was passed over the palladised charcoal catalyst, which was maintained at a temperature of 280°C, in a stream of hydrogen (80 ml/min.) and 2,4,6-trifluoropyridine was obtained in approximately 75% of the theoretical yield, [Found: C, 44.7, H, 1.67, F, 43.3%, $C_5H_2NF_3$ requires C, 45.1, H, 1.51, F,42.9%].

It was confirmed by examination of the ^1H and ^{19}F nuclear magnetic resinous spectra that the hydrogen atoms were at positions 3 and 5 of the pyridine ring system.

Example 3

Reduction of Pentafluoropyridine

When pentafluoropyridine was passed in a stream of hydrogen (50 ml/min.) over palladised charcoal at a temperature of 310°C, the product of the reduction contained 2,3,5,6-tetrafluoropyridine (~40%) and starting material (~60%). This percentage conversion can be improved by variation of the temperature of the reaction and the hydrogen flow-rate.

The 2,3,5,6-tetra fluoropyridine was separated by vapour phase chromotography (v.p.c.). The hydrogen atom was shown to be in position 4 by examination of the n.m.r. spectrum and, on analysis, it gave C, 39.9%, C_5NHF_4 requires C, 39.74%.

Example 4

Preparation of 3,4,5,6-tetrafluoropyridine

Pentafluoropyridine (5 g.) was flash distilled at 180°C. over two hours in a steam of hydrogen (60 ml/min) and the vapour was carried in the gas stream through a silica tube packed with palladised charcoal (10% Pd, 90% C) heated at 300°C. The product (2.6 g.) was condensed dried by distillation under vacuum from phosphorus pentoxide and then separated by v.p.c. It contained 2,3,5,6-tetrafluorpyridine (30% of theoretical yield), b.p. 98—99°C (found C, 39.9%; mol. wt. 152. C_5HF_4N requires C, 39.7%; mol. wt. 151); 3,4,5,6-tetrafluoropyridine (5% of theoretical yield) b.p. 87—88°C (found: C 39.5%, F, 50.2%. C_5HF_4N requires C, 39.7% F, 50.3%), and another minor component which was probably 2,4,5,6-tetrafluoropyridine.

Example 5

Preparation of 2,4,5,6-Tetrafluoronicotinic Acid

Butyl lithium (0.0033 mole) in hexane solution (1 ml) was added with stirring to

2,4,5,6-tetrafluoropyridine (0.5 g. 0.0033 mole) in hexane (2 ml) which was cooled to −60°C. The temperature must not be lower than −65°C otherwise the starting material is thrown out of solution. While maintaining the temperature at −60°C, dry carbon dioxide was passed into the reaction mixture for 30 minutes. The reaction mixture was then allowed to warm up to room temperature while the introduction of CO_2 continued. A white precipitate formed; this dissolved when water (5 ml) was added. Aqueous hydrochloric acid (5 ml) was then added and a precipitate formed which redissolved immediately. The mixture was extracted with ether and the ethereal layer was separated and dried ($MgSO_4$). The solvent was distilled leaving white crystals of 2,4,5,6-tetrafluoronicotinic acid (0.3 g.). This was purified by vacuum sublimation and recrystallisation from hexane and had m.p. 121.5—122°C. Found: C, 37.1, F, 38.6%; C_5NF_4COOH requires C, 36.95, F, 38.98%.

EXAMPLE 6

Preparation of 2,4,6-trifluoronicotinic acid

2,4,6-Trifluoropyridine (0.425 gm., 0.0032 moles) was dissolved in dry hexane (6 c.c) and cooled to −60°C. Butyl lithium (0.0064 moles) in hexane (2 c.c.) was added slowly, with stirring, to the cooled solution. The reaction mixture was maintained at −60°C., and after 15 minutes, when a dense white precipitate had formed, dry CO_2 was passed into it, and the mixture was allowed to warm up to room temperature while CO_2 continued to pass. Water (5 c.c), followed by dilute HCl solution (20 c.c) was then added, the organic layer was separated and the aqueous layer was extracted with ether. The hexane solution and the etheral extracts were combined and dried ($MgSO_4$). The solvents were removed leaving a white crystalline residue (0.4 gm.). The solid sublimed readily at 55°C. *in vacuo*. Recrystallisation from hexane yielded white needles. m. pt. 125—126°C. Yield 65% of theoretical.

$C_6NF_3O_2H_3$ requires: C=40.6%, H=1.13%, F=32.2%
found: C=40.3%, H=1.28% F=32.2%

EXAMPLE 7

Preparation of 3,5-dicarboxy-2,4,6-trifluoropyridine

2,4,6-Trifluodopyridine (0.85 gm., 0.0064 moles) in dry tetrahydrofuran (3 c.c) was added slowly to a stirred solution of butyl lithium (0.0192 moles) in hexane (6 c.c.) and tetrahydrofuran (10 c.c.) at −75°C. After 5 minutes a dense pale orange precipitate formed, and the temperature was maintained at −75°C. for a further 15 minutes when dry CO_2, diluted with an equal volume of nitrogen, was passed into the reaction mixture. Initially, a dark crimson colour was formed which turned very dark brown, and the reaction mixture solidified to a stiff paste. Continued passage of CO_2 caused the dark colour to disappear and, as the temperature was allowed to rise to that of the room, the reaction mixture became more fluid. When the reaction mixture attained room temperature, the passage of CO_2 was stopped and water (10 c.c) followed by dilute HCl solution (50 c.c.) was added. The mixture was extracted with ether (2×25 c.c.), the organic extracts were dried ($MgSO_4$), and the solvent was removed leaving a solid residue (0.6 gm.). The solid was heated at 50°C. *in vacuo* and a white solid (0.25 gm.) sublimed. The infra-red spectrum and m. pt. of this compound were identical to those of an authentic specimen of 2,4,6-trifluoronicotinic acid. The remaining solid was washed with benzene, filtered and heated at 140°C. *in vacuo* when it was observed to sublime slowly. The infra-red spectrum of this sublimate showed the presence of a very strong absorption band at 5.8μ as well as those indicating the presence of —OH and a fluoropyridine nucleus. Analysis of this compound showed it to be the desired product:

$C_7NF_3O_4H_2$ found: C=38.2% H=0.87% F=25.5%
requires: C=38.1% H=0.9% F=25.7%

EXAMPLE 8

Preparation of 2,3,5,6-tetrafluoroisonicotinic acid

Butyl lithium (3.3. m. moles) in hexane (1 ml.) was added to 2,3,5,6-tetrafluoropyridine (0.5 g., 3.3. m. moles) in hexane (18 ml.) at −55°C. under an atmosphere of dry nitrogen. After 20 minutes a precipitate had formed and then the temperature was lowered to −60°C. Dry carbon dioxide was passed into the reaction mixture for 30 minutes. The mixture was allowed to warm up to room temperature while the introduction of carbon dioxide continued. After the mixture had reached room temperature water (5 ml.) was added, followed by dilute hydrochloric acid (5 ml.). The mixture was then extracted with ether. The etheral solution was dried ($MgSO_4$) and the solvent was removed by distillation. 2,3,5,6-Tetrafluoroisonicotinic acid (0.32 g., 50% of theoretical yield) was obtained which, after vacuum sublimation and recrystallisation (hexane), gave m.p. 102—103°C. (found: eq.

wt. 192. Calculated for $C_6HF_4O_2N$, eq. (wt. 195). The infra-red spectrum and m.p. were identical with those of an authentic specimen of the acid.

EXAMPLE 9

Analysis and identification of 2,5,6- trifluoropyridine

B. pt. 115—116°C. (found: C,45.2%; F, 42.6%; $C_5H_2F_3N$ requires C, 45.1%; F, 42.9%). The fluorine-19 n.m.r. spectrum showed three chemically shifted peaks of equal intensity, two of which were broad and to low field, indicating the proximity to the ^{14}N nucleus.

δ=74.40 (2—F); 89.69 (6—F); and 147.4 (5—F).

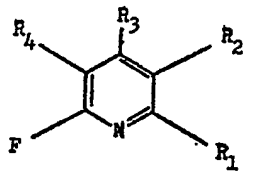
EXAMPLE 10

Preparation of tetrafluoropicolinic acid

2,3,4,5-tetrafluoropyridine (0.3 gm., 1.8 m moles) was dissolved in dry ether (10 ml.). The solution was cooled to −78°C., and then n-butyl lithium (3.0 m moles) in a mixed solvent [hexane (1 ml.) diethyl ether (5 ml.)] was added slowly with stirring; the temperature being kept at −78°C. A deep purple colour was formed as the temperature was allowed to rise to −70°C. and maintained there for 15 minutes. Dry carbon dioxide was passed into the reaction mixture and the temperature was allowed to rise to that of the room with continued passage of carbon dioxide. Water (5 ml.) followed by dilute HCl (10 ml.) was added, and the reaction mixture was transferred to a separating funnel where concentrated HCl (10 ml.) was added. The mixture was extracted with ether, the etheral extracts were dried ($MgSO_4$) and filtered, and the solvent was removed by distillation leaving a viscous brown liquid residue. This liquid was heated *in vacuo* and a white solid sublimed at 50°C. Crude yield 0.2 gm. (57%). This solid was recrystallised from hexane, giving pure tetrafluoropicolinic acid. M. pt. 109—110°C. (Found: C,36,9% $C_6HF_4NO_2$ requires C, 36.9%).

WHAT WE CLAIM IS:—

1) A process for the production of a fluoropyridine carboxylic acid or dicarboxylic acid of the formula



wherein one of the symbols R_1, R_2 and R_3 represents a carboxy group whilst the remaining symbols represent fluorine atoms, and R_4 represents a fluorine atom or when R_2 represents a carboxy group, R_4 can represent a flourine or hydrogen atom or a carboxy group, which process comprises converting 2,4,6-trifluoropyridine or a tetrafluoropyridine into the corresponding lithium derivative at a low temperature, reacting the lithium derivative with carbon dioxide, and hydrolysing the resulting product.

2) A process as claimed in claim 1 substantially as hereinbefore described.

3) A process as claimed in claim 1 substantially as described with reference to any of Examples 5 to 8 or 10.

4) Fluoropyridine carboxylic or dicarboxylic acids when prepared by a process as claimed in any of the preceding claims.

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